CC: 12/30/83

RA Fisher.

May 18, 1948.

Dear Dr. Fisher,

You may be interested in the method used for estimating the absolute distances referred to on p. 515. This is largely an intellectual exercise because a) the data are so heterogeneous, and b) no-interference is assumed, but it was the best I could do. Summing the classes in Table 5 which refer to interchanges in a given region (C,D, and E) we have the totals:

C	D	E	triples	
817	1389	828	63	3097
(.264)	(.448)	(.268)	(.020)	1.000

Taking $y = \sinh x$ as the relationship between recombination fraction and map distance (i.e. no interference, and a Poisson distribution of crossovers) a set of equations symmetrical with $\tanh^2 x_3 = (.020)(.264) / (.448)(.268)$ is readily derived. The sum of C,D and E is found to be about 80 centimorgans. I am looking for triple-crossing-over data reported for other organisms with which to make an empirical adjustment for interference; do you know of any showing about 2% ?

I would appreciate an exchange of publications dealing with the stimation of map distance and the theory of recombination.

Yours respectfully,

Joshua Lederberg
Assistant Professor of Genetics.

supplemented agar is homogeneous with the distribution in prototrophs, so that the segregation of these factors is not influenced by the B_1 segregation.

The data in table 5 show that *Lac* is inclined not to separate from *BM*, and is therefore regarded as linked to it, while there is a similar linkage of V_1 to *TL*. Since the recombination of *Lac* with *BM* is not influenced by the interchange between B_1 and *BM*, they are on opposite sides of *BM* as suggested by map 2b. Finally, a scrutiny of the interaction between the *Lac* and *V* segregations shows that these are not independent of each other, particularly because of the rarity of the least frequent class. This suggests, then, that the two linkage groups of fig. 2b be combined to give the map of fig. 2c. (The locus of V_6 on this map is obtained from additional data.) According to this interpretation, the rarity of the least frequent *Lac-V* combination stems from the fact that a triple-crossover is necessary for its production. In fig. 2d, the cross Y-40×Y-53 is interpreted according to the map, with a table citing the regions in which interchange must take place to yield the given types.

That the first seven factors to be investigated should fall in the same linkage group leads to the inference that there is only a single chromosome in *E. coli*. This inference is supported by incomplete analyses of the segregations of 8 other markers referred to in table 1. None of these factors has been found to segregate independently of the factors which have already been described as belonging to a single linkage group. The possibility that segregation interactions may, in some cases, be based upon an inter-chromosomal type of interference (compare STEINBERG and FRASER, 1944), has not been ruled out, however.

The distances recorded in fig. 2c are derived from the recombination totals in tables 5 and 6. However, the distance between [*BM*] and [*TL*] cannot be estimated directly, but only the partition of that distance among the regions *BM-Lac*, *Lac-*V_1, and V_1-*TL*. The relative frequency of the "triple-interchange" type can be used to estimate the absolute map distances, if it is assumed that there is no interference. This frequency, about 2.1 percent, is readily calculated to be consistent with a map length of between 75 and 80 units altogether either in a two-strand or a four-strand system (LEDERBERG, 1947). These values must be regarded as rough approximations, because they are extremely sensitive to error in the estimation of the proportion of the "triple" types.

Linearity

In constructing a map, and calculating distances, it has been taken for granted that there is in *E. coli* a system of linear linkage, such as has been demonstrated quite conclusively in Drosophila, and inferred in all higher organisms. What direct evidence may one bring to bear on this question?

The method which one is forced to employ in hybridizing this bacterium introduces certain complications. The classical proof of linearity is based on the additive character of distances, expressed in morgans, between loci occurring within the same linkage group. The determination of map distances is based upon a comparison between parental and new combinations of linked